

Description

This invention relates to a novel chemical process for preparing aryl-piperidine carbinols and to novel intermediates used in that process.

British patent no. 1422263 and US patent no 4007196 disclose compounds of formula A

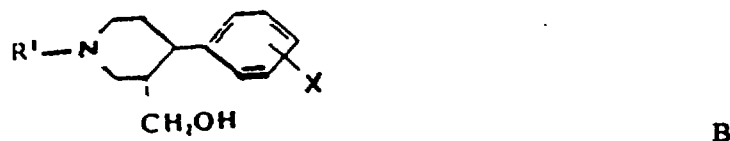


in which R¹ represents hydrogen, trifluoro (C₁₋₄) alkyl, alkyl or alkynyl, R² represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C₁₋₄ alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl, and X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio, or aralkyloxy.

The compounds of formula A are disclosed as having pharmacological properties that make them useful as anti-depressants.

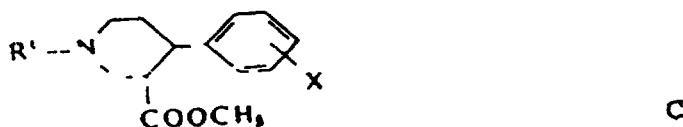
One compound that has proved especially valuable is paroxetine [R¹ = H, R² = 5-(1,3-benzdioxyl), X = 4-F] which is in the (-)-trans configuration.

In the above-mentioned patents, the compounds of formula A are prepared using an intermediate of formula B



in which R¹ and X are as defined above.

The piperidine carbinols of formula B are prepared by reduction of an ester of formula C



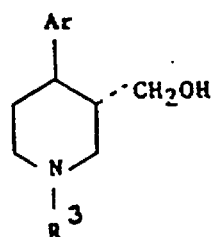
with a complex metal hydride reducing agent.

The compound of formula C is obtained by reacting arecoline (when R¹ = methyl) or arecoline homologues with phenyl (or substituted phenyl) magnesium bromide.

This procedure has the disadvantage that arecoline is a powerful irritant and that the ester of formula C is obtained as a mixture of cis and trans configuration compounds.

We have now discovered a new process for preparation of piperidine carbinols which advantageously avoids the use of arecoline and selectively produces the trans-isomer in a good overall yield.

Accordingly, the present invention provides a process for preparing a compound of formula I

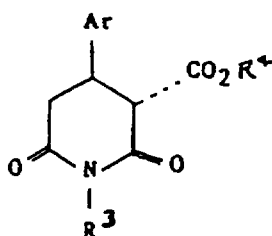


I

in which Ar represents a group



where X is as defined for formula A and R³ represents hydrogen, an alkyl or aralkyl group, by reduction of a compound of formula II



II

in which Ar and R³ are as defined for formula (I), and R⁴ is an alkyl group.

Preferably X is fluorine or hydrogen, R³ is hydrogen, methyl or benzyl, and R⁴ is ethyl.

The reduction may be carried out conventionally using a metal hydride, for example using lithium aluminium hydride or aluminium hydride in an inert solvent such as tetrahydrofuran or in a tetrahydrofuran/toluene mixture.

The compounds of formula I are obtained in the trans configuration but as a mixture of enantiomers. The compounds may be resolved into their enantiomeric forms by conventional methods, such as by use of an optically active acid, for example (+)-2'-nitrotartronic acid or (-)-di-p-toluoyletartaric acid.

The compounds of formula I may be used as intermediates in the preparation of compounds of formula A making use of the procedures set out in British Patent no 1422263 or US patent no 4007196.

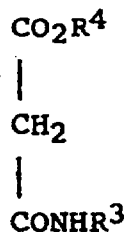
For example, to prepare paroxetine, the compound of formula I in which Ar =



and preferably R³ = Me to protect the nitrogen atom, in the (-)-trans -configuration, is reacted with thionyl chloride or benzenesulphonyl chloride and then with sodium 3,4-methylenedioxyphenoxide. Subsequently the N-methyl group is replaced by reaction with phenyl chloroformate followed by de-acylation with KOH to obtain R³ = H.

The present invention also provides certain intermediates of formula II as novel compounds. Preferred substituents are as exemplified for formula I.

The compounds of formula II may be prepared by reaction of appropriate cinnamic acid esters, such as alkyl and aryl esters, and alkyl amido-malonates of formula III where R³ and R⁴ are as defined previously.



III

The reaction may be performed as a condensation in a base/solvent system, for example sodium hydride/dimethyl sulphoxide; potassium tert. butoxide in ethanol or tetrahydrofuran; or sodium methoxide or ethoxide in ethyl acetate.

Advantageously the compound of formula II is prepared as a 'single pot' reaction forming the cinnamate in situ from the appropriate benzaldehyde. For example the appropriate alkyl amidomalonate is added to a mixture of the benzaldehyde and sodium methoxide in ethyl acetate.

Compounds of formula II in which $\text{R}^3 = \text{alkyl}$ or aralkyl may also be prepared by conventional alkylation of compounds of formula II in which $\text{R}^3 = \text{H}$. For example, ester-imides of formula II in which $\text{R}^3 = \text{H}$ may be reacted with alkyl or aralkyl halides in the presence of mild bases such as potassium carbonate.

The above described processes for producing the novel intermediates of formula II also form part of this invention.

As used herein, the terms alkyl, aryl, aralkyl, alkoxy and aralkyloxy include, but are not limited to, groups in which the alkyl moiety, if present, is straight or branched and contains from 1 to 6 carbon atoms, more especially from 1 to 4 carbon atoms, and the aryl moiety, if present, is phenyl.

The following Examples illustrate the preparation of novel intermediates of this invention (Examples 1 to 4) and the novel process of this invention (Examples 5 to 9). Temperatures are in $^{\circ}\text{C}$.

Example 1

(±)-trans-3-Ethoxycarbonyl-4-(4'-fluorophenyl) piperidin-2,6-dione (E1)

Potassium t-butoxide (1.01g) was added to a solution of ethyl amidomalonate (1.38g) in tetrahydrofuran (38ml) maintained at 33° . After cooling to 25° , ethyl 4-fluorocinnamate (1.50g) was added and the mixture stirred overnight at room temperature. Brine was added, the mixture extracted with ethyl acetate (3 x 60 ml) and the organic solution dried and evaporated to give the crude product. This was chromatographed on silica gel, using dry ether as eluent, to give the title compound (0.92g, 43%), m.p. $97-99^{\circ}$.

$^1\text{H-n.m.r.}$ (CDCl_3)

$\delta =$ 1.07 (t, $J = 8\text{Hz}$, 3H)
 2.67-2.90 (m, 2H)
 3.50-3.84 (m, 2H)
 4.00 (q, $J = 8\text{Hz}$, 2H)
 6.70-7.27 (m, 4H)
 8.90 (br.s, 1H)

Example 2

(±)-trans-3-Ethoxycarbonyl-4-(4'-fluorophenyl)-N-methyl piperidin-2,6-dione (E2)

(a) Sodium hydride (80%, 2.6g) was added slowly to a stirred solution of ethyl N-methylamidomalonate (11.9g) in dimethyl sulphoxide (50ml) under nitrogen. After hydrogen evolution had ceased and the dark solution had cooled to room temperature, ethyl 4-fluorocinnamate (15.3g) was added in one portion along with further dimethyl sulphoxide (10ml) and the whole stirred at room temperature for 19 hours. After extraction with petroleum ether (3 x 16ml), the mixture was stirred and neutralised by the addition of glacial acetic acid (4.9ml) followed by the addition of ethyl acetate (75ml) and water (35ml). The organic solution was separated, washed with brine (30 ml), sodium bicarbonate solution (22ml) and brine and finally dried over anhydrous sodium sulphate. Evaporation gave an off-white crystalline solid (22.7g), which was

titrated with isopropyl ether before filtering and drying to give the title compound as a white crystalline solid (20.0g, 86%), m.p. 91-96°.

¹H-n.m.r. (CDCl₃)

6 δ = 1.10 (t, J=8Hz, 3H)
 2.75-3.00 (m, 2H)
 3.18 (s, 3H)
 3.50-3.90 (m, 2H)
 10 4.10 (q, J=8Hz, 2H)
 6.80-7.30 (m, 4H)

15 (b) A solution of compound E1 (±)-trans-3-ethoxycarbonyl-4-(4'-fluorophenyl)piperidin-2,6-dione (1.0g) in anhydrous dimethylformamide was stirred and cooled to about 0° and methyl iodide (0.67g) and anhydrous potassium carbonate (0.51g) added. The mixture was stirred at 0-2° for 7.5 hours, after which it was diluted with water and extracted with ethyl acetate (100ml). The extract was washed with water, brine and dried over anhydrous sodium sulphate. Evaporation gave the title compound as a pale yellow oil, ca. 90% pure by n.m.r. spectroscopy.

Example 3

20 (±)-trans-3-Ethoxycarbonyl-4-(4'-fluorophenyl)-piperidin-2,6-dione (E3)

25 A solution of ethyl amidomalonate (17.5 gms, 1.0 eq at 70%) in ethyl acetate (50 ml) was added to a solution of ethyl cinnamate (21.6 gms, 0.1m at 90%) in ethyl acetate (200 mls) containing sodium methoxide (7.6 gms) over 0.5 hr at 20°C. The slurry was stirred for 8 hours at 20°C and 72 hours at 5°C. The slurry was then added to a mixture of water (200 ml) and acetic acid (2.5 eq).

After separation of the rich ethyl acetate the solvent was evaporated under reduced pressure and product isolated via crystallisation from propan-2-ol by adding heptane.

30 Yield = 5.2 gms

Product was a mixture of 20% methyl, 80% ethyl esters

Structure confirmed by NMR and HPLC comparison with the N-methyl equivalent. (E2)

35 Example 4

(±)-trans-3-Ethoxycarbonyl-4-(4'-fluorophenyl)-N-methyl-piperidin-2,6-dione (E4)

40 A solution of p-fluorobenzaldehyde (100g) in ethyl acetate (100ml) was added slowly to a mixture of sodium methoxide (105g) in ethyl acetate (900ml), maintaining the temperature at 10-20°C and stirring for a further 30 minutes at 15-25°C. Then a solution of desiccated ethyl N-methylamidomalonate (139g) in ethyl acetate (200ml) was added over 1 hour whilst maintaining the temperature at 15-25°C and stirring for a further 1-2 hours. The resulting mixture was added to solution of acetic acid (120g) in water (475ml) and
 45 stirred for 15 minutes. The lower aqueous layer was then separated and discarded. The rich solvent was washed with saturated brine (250ml). The solvent was removed by vacuum distillation and replaced with propan-2-ol then cooled with stirring to obtain the crystalline title compound. Water (600ml) was added over 30 minutes and the mixture stirred for 1-2 hours at 15-25°C. The product was filtered and washed with water then isopropyl ether before drying.

50 Yield = 80-90%

Example 5

55 (±)-trans-4-(4'-Fluorophenyl)-3-hydroxymethyl-N-methyl-piperidine (E5)

Compound E2 (±)-trans-3-ethoxycarbonyl-4-(4'-fluorophenyl)-N-methylpiperidin-2,6-dione (18.0g) in tetrahydrofuran (80ml) was added slowly to a solution of lithium aluminium hydride (6.0g) in tetrahydrofuran

(40ml) under nitrogen, keeping the temperature below 40°. When addition was complete, the reaction mixture was stirred at room temperature overnight, then warmed to 50° for about 7 hours and finally stirred overnight at room temperature.

Decomposition was effected by the careful addition of water (30ml) followed by 10% aqueous sodium hydroxide solution (6.0ml). The hydrolysed mixture was stirred for 1½ hours before filtering off the precipitated salts which were washed with ethyl acetate (50ml). The filtrate was dried over anhydrous sodium sulphate and evaporated down to give a solid product which was triturated with ether, filtered and dried, to give the title compound (9.0g, 65%), m.p. 122-126°.

10. ¹H-n.m.r (DMSO-d₆)

δ = 1.56-1.92 (m, 5H)
2.15-2.29 (m, 4H)
2.77-2.85 (d, 1H)
2.88-2.99 (m, 1H)
3.02-3.14 (m, 2H)
3.38 (s, 1H)
7.06-7.29 (m, 4H)

20. Resolution

The title compound E5 (8.6g) and (+)-2'-nitrotartronic acid (10.4g) were dissolved in warm acetone (70ml) and water (1.9ml) added. After cooling and allowing to stand at 5° for 2 days, the crystalline salt was filtered off, washed with acetone and dried *in vacuo* (7.7g, 39%).

The salt (7.6g) was suspended in water and a slight excess of dilute hydrochloric acid added to precipitate the tartronic acid which was filtered off and washed with water. The filtrate was basified with sodium carbonate solution and extracted with ethyl acetate (total 60ml) and the extracts washed with sodium carbonate solution, water and dried over anhydrous sodium sulphate. Evaporation gave (-)-trans-4-(4'-fluorophenyl)-3-hydroxymethyl-N-methylpiperidine as a crystalline solid which was triturated with ether/petroleum ether (b.p. 60-80°), filtered and dried (3.1g, 95% recovery), m.p. 102-103° [α]_D²⁶ (c=5 in acetone) -37°.

Example 6

35. (±)-trans-4-(4'-Fluorophenyl)-3-hydroxymethylpiperidine

Compound E1 (±)-trans-3-ethoxycarbonyl-4-(4'-fluorophenyl)piperidin-2,6-dione (2.0g) was reduced with lithium aluminium hydride (0.58g) in refluxing tetrahydrofuran (50ml) for 4 hours. Work up as described in Example 5 gave the title compound as a solid (0.28g, 22%).

Example 7

(±)-trans-4-(4'-fluorophenyl)-3-hydroxymethyl-N-methyl piperidine. (E7)

Compound E4 (34g) in toluene (150 ml) was added slowly to a slurry of lithium aluminium hydride (10g) in a tetrahydrofuran (50 ml)/toluene (150 ml) mixture, maintaining the temperature at 0-5° C under nitrogen. (Commercially available solutions of lithium aluminium hydride in tetrahydrofuran/toluene have also been used successfully). The mixture was stirred for a further 1-5 hours and then allowed to warm up to 15-25° C overnight. The excess lithium aluminium hydride was destroyed by the carefully controlled addition of water (10 ml), dilute 15% sodium hydroxide (10 mls) and water (30 ml). The solids were then removed by filtration and reslurried in toluene (100 ml). The combined rich toluene layers were concentrated to a low volume (75 ml) and poured into petroleum ether [100-1200] (25 ml). After stirring for 8-24 hours the product was isolated by filtration, washed with petroleum ether (10 ml) and dried.

Yield = 65-75%

Example 8

(-)-trans-4-(4'-Fluorophenyl)-3-hydroxymethyl-N-methyl piperidine

Compound E7 (5g) was dissolved in acetone (50 ml) and added to a solution of (-)-di-p-toluoyltartaric acid ((11.25g) in acetone (50 ml) at 15-25 °C. The mixture was stirred for 1 hour at 15-25 °C, then a further 5 hour at 0-10 °C. The crystalline salt was filtered off, washed with acetone and dried.

Yield = 40-45%

10 The salt (6g) was suspended in water and methylene dichloride (MDC). The (-)-trans-4-(4'-fluorophenyl)-3-hydroxymethyl-N-methylpiperidine was extracted into the MDC using sodium hydroxide. Evaporation of the rich MDC gave an oil which was redissolved in toluene. The toluene was removed by evaporation to give an oil. The addition of heptane and trituration gave a crystalline solid which was filtered off and dried.

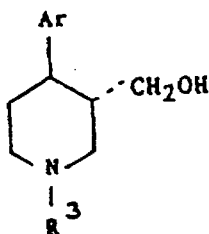
15 Yield = 85-89% $[\alpha]_D^{26} = -35^\circ$ (c=1% in methanol).

Example 9(±)-trans-4-(4'-Fluorophenyl)-3-hydroxymethyl-N-methyl piperidine (E9)

20 Lithium aluminium hydride (3.24g; 0.085 mol) was added with stirring to dry tetrahydrofuran (200ml) at 0 °C under an atmosphere of nitrogen. Concentrated sulphuric acid (2.16ml) was then added dropwise and the mixture stirred at 0 °C for 1 hour to give a solution of aluminium hydride. The imide (E2, 10.0g; 0.034 mol) was added as a solution in dry tetrahydrofuran (199ml) and the mixture stirred at 0-5 °C for 4-5 hours, 25 then at room temperature overnight. Sodium hydroxide (16.2ml of a 40% aqueous solution) was added, and the resultant precipitate was filtered and washed. Filtration was repeated several times to remove cloudiness then the filtrate and washing were evaporated in vacuo, to give the product as an orange oil (6.9g, 91%) which could be crystallised from ether, m.p. 122-3 °C.

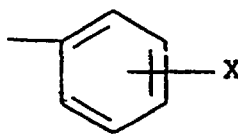
30 Claims

1. A process for the preparation of a compound of formula (I):



(I)

45 wherein Ar is a group



50 where X represents hydrogen, C₁₋₄ alkyl, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy and R³ is hydrogen, alkyl or aralkyl, which process comprises reducing a compound of formula (II):

55

(-)-trans-4-(4'-Fluorophenyl)-3-hydroxymethyl-N-methyl piperidine

Compound E7 (5g) was dissolved in acetone (50 ml) and added to a solution of (-)-di-p-toluoyletartaric acid ((11.25g) in acetone (50 ml) at 15-25 °C. The mixture was stirred for 1 hour at 15-25 °C, then a further hour at 0-10 °C. The crystalline salt was filtered off, washed with acetone and dried.

Yield = 40-45%

The salt (6g) was suspended in water and methylene dichloride (MDC). The (-)-trans-4-(4'-fluorophenyl)-3-hydroxymethyl-N-methylpiperidine was extracted into the MDC using sodium hydroxide. Evaporation of the rich MDC gave an oil which was redissolved in toluene. The toluene was removed by evaporation to give an oil. The addition of heptane and trituration gave a crystalline solid which was filtered off and dried.

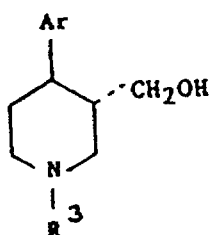
Yield = 85-89% $[\alpha]_D^{26} = -35^\circ$ (c=1% in methanol).

Example 9(±)-trans-4-(4'-Fluorophenyl)-3-hydroxymethyl-N-methyl piperidine (E9)

Lithium aluminium hydride (3.24g; 0.085 mol) was added with stirring to dry tetrahydrofuran (200ml) at 0 °C under an atmosphere of nitrogen. Concentrated sulphuric acid (2.16ml) was then added dropwise and the mixture stirred at 0 °C for 1 hour to give a solution of aluminium hydride. The imide (E2, 10.0g; 0.034 mol) was added as a solution in dry tetrahydrofuran (199ml) and the mixture stirred at 0-5 °C for 4-5 hours, then at room temperature overnight. Sodium hydroxide (16.2ml of a 40% aqueous solution) was added, and the resultant precipitate was filtered and washed. Filtration was repeated several times to remove cloudiness then the filtrate and washing were evaporated in vacuo, to give the product as an orange oil (6.9g, 91%) which could be crystallised from ether, m.p. 122-3 °C.

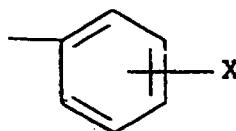
Claims

1. A process for the preparation of a compound of formula (I):



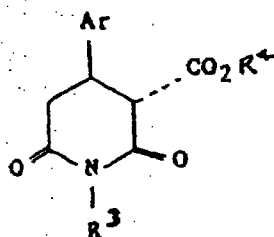
(I)

wherein Ar is a group



where X represents hydrogen, C_{1-4} alkyl, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy and R^3 is hydrogen, alkyl or aralkyl, which process comprises reducing a compound of formula (II):

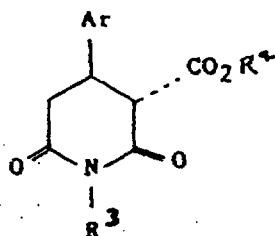




(II)

wherein Ar and R³ are as defined with respect to formula (I) and R⁴ is alkyl.

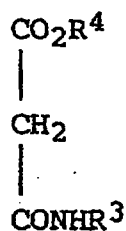
2. A process according to claim 1, wherein the reduction is carried out with a metal hydride reducing agent.
3. A compound of formula (IIA), for use in the process according to claim 1 or 2,



(IIA)

wherein Ar, R³ and R⁴ are as defined in claim 1, with the proviso that when R³ is hydrogen or methyl, R⁴ and Ar are not ethyl and phenyl respectively.

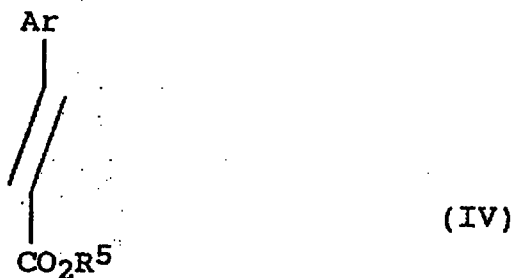
4. A compound according to claim 3, for use in the process according to claim 1 or 2, which is ($\pm$)-trans-3-ethoxycarbonyl-4-(4'-fluorophenyl)-piperidin-2,6-dione, ($\pm$)-trans-3-ethoxycarbonyl-4-(4'-fluorophenyl)-N-methyl piperidin-2,6-dione, or ($\pm$)-trans-3-methoxycarbonyl-4-(4'-fluorophenyl)-piperidin-2,6-dione.
5. A process for the preparation of a compound of formula (I) as defined in claim 1, which process comprises (a) reacting a compound of formula (III):



(III)

wherein R³ and R⁴ are as defined in claim 1, with a compound of formula (IV):





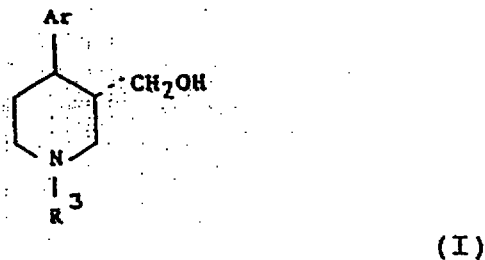
wherein Ar is as defined in claim 1 and OR^5 is a leaving group, to form a compound of formula (II) as defined in claim 1, and subsequently, if desired, converting a compound of formula (II) wherein R^3 is hydrogen to a compound of formula (II) wherein R^3 is alkyl or aralkyl; and

(b) reducing the compound of formula (II) thereby formed to a compound of formula (I).

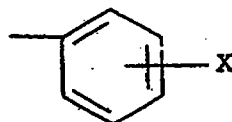
6. A process according to claim 5, wherein a compound of formula (III) as defined in claim 5 is condensed with a compound of formula (IV) as defined in claim 5 in a base/solvent system.
7. A process according to claim 5 or 6, wherein a compound of formula (II) wherein R^3 is hydrogen is converted to a compound of formula (II) wherein R^3 is alkyl or aralkyl by reaction with an alkyl or aralkyl halide in the presence of a base.
8. A process according to claim 5, 6 or 7, wherein a compound of formula (IV) as defined in claim 5 is formed in situ by the base catalysed condensation of a compound of formula $ArCHO$ with an ester of acetic acid.

Revendications

1. Procédé pour la préparation d'un composé de formule (I) :

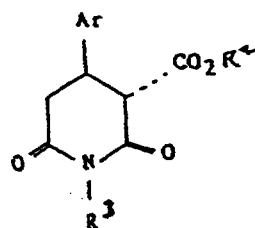


dans laquelle Ar est un groupe



où X représente un atome d'hydrogène, un groupe alkyle en C_{1-4} , alcoxy, trifluoroalkyle, hydroxy, un atome d'halogène, un groupe méthylthio ou aralkyloxy et R^3 est un atome d'hydrogène, un groupe alkyle ou aralkyle, caractérisé en ce qu'il comprend la réduction d'un composé de formule (II) :

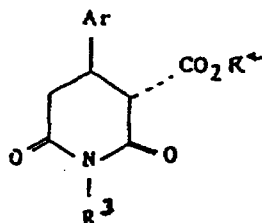




(II)

dans laquelle Ar et R³ sont tels que définis à propos de la formule (I) et R⁴ est un groupe alkyle.

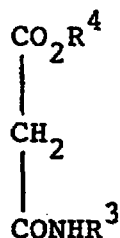
2. Procédé suivant la revendication 1, caractérisé en ce que la réduction est effectuée avec un hydrure métallique en tant qu'agent réducteur.
3. Composé de formule (IIA), caractérisé en ce qu'il est utile dans le procédé suivant la revendication 1 ou 2,



(IIA)

dans laquelle Ar, R³ et R⁴ sont tels que définis dans la revendication 1, à condition que dans le cas où R³ est un atome d'hydrogène ou un groupe méthyle, R⁴ et Ar ne soient pas un groupe éthyle et phényle respectivement.

4. Composé suivant la revendication 3, utile dans le procédé suivant les revendications 1 ou 2, caractérisé en ce qu'il s'agit de la (+)-trans-3-éthoxycarbonyl-4-(4'-fluorophényl)-pipéridin-2,6-dione, la (+)-trans-3-éthoxycarbonyl-4-(4'-fluorophényl)-méthylpipéridin-2,6-dione, ou la (+)-trans-3-méthoxycarbonyl-4-(4'-fluorophényl)-pipéridin-2,6-dione.
5. Procédé pour la préparation d'un composé de formule (I) tel que défini dans la revendication 1, caractérisé en ce qu'il comprend (a) la réaction d'un composé de formule (III) :



(III)

dans laquelle R³ et R⁴ sont tels que définis dans la revendication 1, avec un composé de formule (IV) :





(IV)

dans laquelle Ar est tel que défini dans la revendication 1 et OR^5 est un groupe mobile, pour former un composé de formule (II) tel que défini dans la revendication 1 et ensuite, si cela est désiré, la conversion d'un composé de formule (II) dans laquelle R^3 est un atome d'hydrogène en un composé de formule (II) dans laquelle R^3 est un groupe alkyle ou aralkyle ; et

(b) la réduction du composé de formule (II) pour former un composé de formule (I).

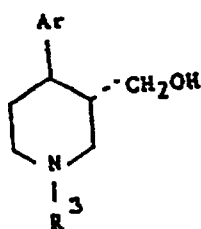
6. Procédé suivant la revendication 5, caractérisé en ce qu'un composé de formule (III) tel que défini dans la revendication 5 est condensé avec un composé de formule (IV) tel que défini dans la revendication 5 dans un système de base/solvant.

7. Procédé suivant la revendication 5 ou la revendication 6, caractérisé en ce qu'un composé de formule (II) dans laquelle R^3 est un atome d'hydrogène est converti en un composé de formule (II) dans laquelle R^3 est un groupe alkyle ou aralkyle par réaction avec un halogénure d'alkyle ou d'aralkyle en présence d'une base.

8. Procédé suivant les revendications 5, 6 ou 7, caractérisé en ce qu'un composé de formule (IV) tel que défini dans la revendication 5 est formé in situ par la condensation catalysée par une base d'un composé de formule $ArCHO$ avec un ester d'acide acétique.

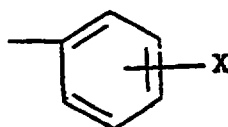
30 Ansprüche

1. Verfahren zur Herstellung einer Verbindung der Formel (I):



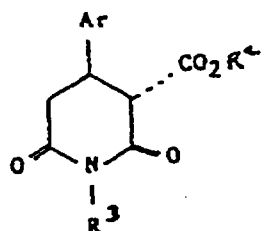
(I)

in der Ar die Gruppe



bedeutet, wobei X ein Wasserstoffatom, einen C_{1-4} -Alkyl-, Alkoxy- oder Trifluoralkylrest, eine Hydroxygruppe, ein Halogenatom, eine Methylthiogruppe oder einen Aralkoxyrest bedeutet und R^3 ein Wasserstoffatom oder einen Alkyl- oder Aralkylrest bedeutet, umfassend die Reduktion einer Verbindung der Formel (II)

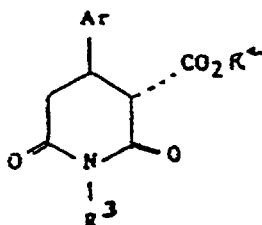




(II)

in der Ar und R³ die in Formel (I) definierte Bedeutung haben und R⁴ einen Alkylrest bedeutet.

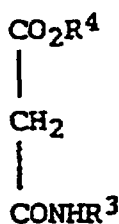
2. Verfahren nach Anspruch 1, in dem die Reduktion mit einem Metallhydrid-Reduktionsmittel durchgeführt wird.
3. Verbindung der Formel (IIA) zur Verwendung in dem Verfahren nach Anspruch 1 oder 2,



(IIA)

wobei Ar, R³ und R⁴ wie in Anspruch 1 definiert sind mit der Maßgabe, daß, falls R³ ein Wasserstoffatom oder eine Methylgruppe bedeutet, R⁴ und Ar nicht eine Ethyl- bzw. Phenylgruppe bedeuten.

4. Verbindung nach Anspruch 3 zur Verwendung im Verfahren nach Anspruch 1 oder 2, nämlich (±)-trans-3-Ethoxycarbonyl-4-(4'-fluorphenyl)-piperidin-2,6-dion, (±)-trans-3-Ethoxycarbonyl-4-(4'-fluorphenyl)-N-methylpiperidin-2,6-dion oder (±)-trans-3-Methoxycarbonyl-4-(4'-fluorphenyl)-piperidin-2,6-dion.
5. Verfahren zur Herstellung einer Verbindung der Formel (I), wie in Anspruch 1 definiert, umfassend (a) die Umsetzung einer Verbindung der Formel (III)



(III)

in der R³ und R⁴ wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel (IV)



(IV)



in der Ar wie in Anspruch 1 definiert ist und OR^5 eine abspaltbare Gruppe bedeutet, zu einer Verbindung der Formel (II) wie in Anspruch 1 definiert, und anschließend gegebenenfalls die Umwandlung einer Verbindung der Formel (II), in der R^3 ein Wasserstoffatom bedeutet, in eine Verbindung der Formel II, in der R^3 einen Alkyl- oder Aralkylrest bedeutet, und
5 (b) eine Reduktion der Verbindung der Formel (II) zu einer Verbindung der Formel (I).

6. Verfahren nach Anspruch 5, wobei eine Verbindung der Formel (III), wie in Anspruch 5 definiert, mit einer Verbindung der Formel (IV), wie in Anspruch 5 definiert, in einem Base/Lösungsmittelsystem kondensiert wird.

10 7. Verfahren nach Anspruch 5 oder 6, wobei eine Verbindung der Formel (II), in der R^3 ein Wasserstoffatom bedeutet, durch Umsetzung mit einem Alkyl- oder Aralkylhalogenid in Gegenwart einer Base, in eine Verbindung der Formel (II), in der R^3 einen Alkyl- oder Aralkylrest bedeutet, umgewandelt wird.

15 8. Verfahren nach Anspruch 5, 6 oder 7, wobei eine Verbindung der Formel (IV), wie in Anspruch 5 definiert, durch eine basenkatalysierte Kondensation einer Verbindung der Formel $ArCHO$ mit einem Ester der Essigsäure in situ gebildet wird.

